10/608,781
Group No.: 1625
U014673-3

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification & Drawing of the extract of Patent Application No.493/MAS/2002, dated 28.06.2002 by Dr. Reddy's Laboratories Limited having its registered office at 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India.

.....

.....**In witness thereof**

I have hereunto set my hand

Dated this the 26th day of December 2003
5th day of Pausa, 1925(Saka)

M. S. V

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
No.443, Anna Salai, Teynampet,Chennai – 600 018

FORM 1

THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7and Rule 33A)

We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

1. (a) that we are in possession of an invention titled "**A Process for the preparation of an amorphous form of Esomeprazole**"
   (b) that the complete specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to us.
2. further declare that the inventors for the said invention are **Manne Satyanarayana Reddy, Muppa Kishore Kumar, Koilkonda Purandhar and Keshaboina Sreenath.** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh.**
3. that we are the assignee of the true and first inventors
4. that our address for service in India is as follows;

   Dr. Manne Satyanarayana Reddy,
   Vice President-R&D
   Dr. Reddy's Laboratories Limited
   7-1-27, Ameerpet
   Hyderabad, A.P., 500 016
5. following declaration was given by the inventors.
   We, the true and first inventors for this invention declare that the applicant herein is our assignee

Signed)_____
Manne Satyanarayana Reddy,
H.No. 8-3-167/D/16,
Kalyan Nagar,
Near AG Colony,
Erragadda, Hyderabad-500 038.

Signed)_____
Muppa KishoreKumar,
LIG-34, Dharma Reddy Colony,
Phase-I,
KPHB,
Hyderabad-500 072.

Signed) K. Purandhar

Koilkonda Purandhar,
MIG – 129,
Balaji Nagar,
Kukatpally,
Hyderabad – 500 072.

Signed) K. Sreenath.

Keshaboina Sreenath,
H.No. 2-8-92,
Waddepally,
Warangal – 506 370.

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. following are the attachments with the application
   (a) complete specification (---12--- pages, in triplicate)
   (b) abstract of the invention (---01--- page, in triplicate)
   (c) drawings (---01--- pages, in triplicate)
   (d) fee Rs. 5000.00 (five thousand rupees only) in cheque bearing No.336085 dated June 13th 2002 drawn on HDFC Bank Limited, Lakdikapul, Hyderabad

We request that a patent may be granted to us for the said invention

Dated this 27th day of June 2002.

Signed) M. Sumi

Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr. Reddy's Laboratories Limited.

FORM 2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

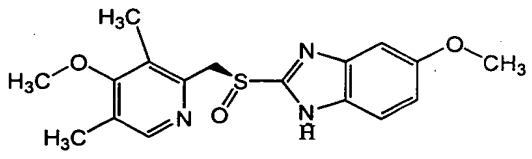
(SECTION 10)

A Process for the preparation of an amorphous form of Esomeprazole

Dr. Reddy's Laboratories ltd
An Indian Company having its registered office at
7-1-27, Ameerpet
Hyderabad – 500 016, A.P., India

The following specification particularly describes the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of an amorphous form of (-) 5-methoxy-2- [[(4-methoxy-3, 5-dimethyl-2-pyridinyl)-methyl] sulphinyl]-1H-benzimidazole, generically known as Esomeprazole. It is represented by the following formula (I).



Formula (I)

Omeprazole, and its therapeutically acceptable alkaline salts are described in EP 5129 and EP 124,495 respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as anitulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom i.e., can exist as an optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties, which will give an improved therapeutic profile.

The separation of the enantiomers of Omeprazole in analytical scale is described in J.Chromatography, 532 (1990), 305-19 and in preparative scale in DE 4035455.

DE 4035455 discloses the process for the preparation of enantiomers of Omeprazole, Esomeprazole and its therapeutically active salts are claimed specifically. The process for the preparation of enantiomers has been done by using diastereomeric ether, which is separated and thereafter hydrolyzed in an acidic solution.

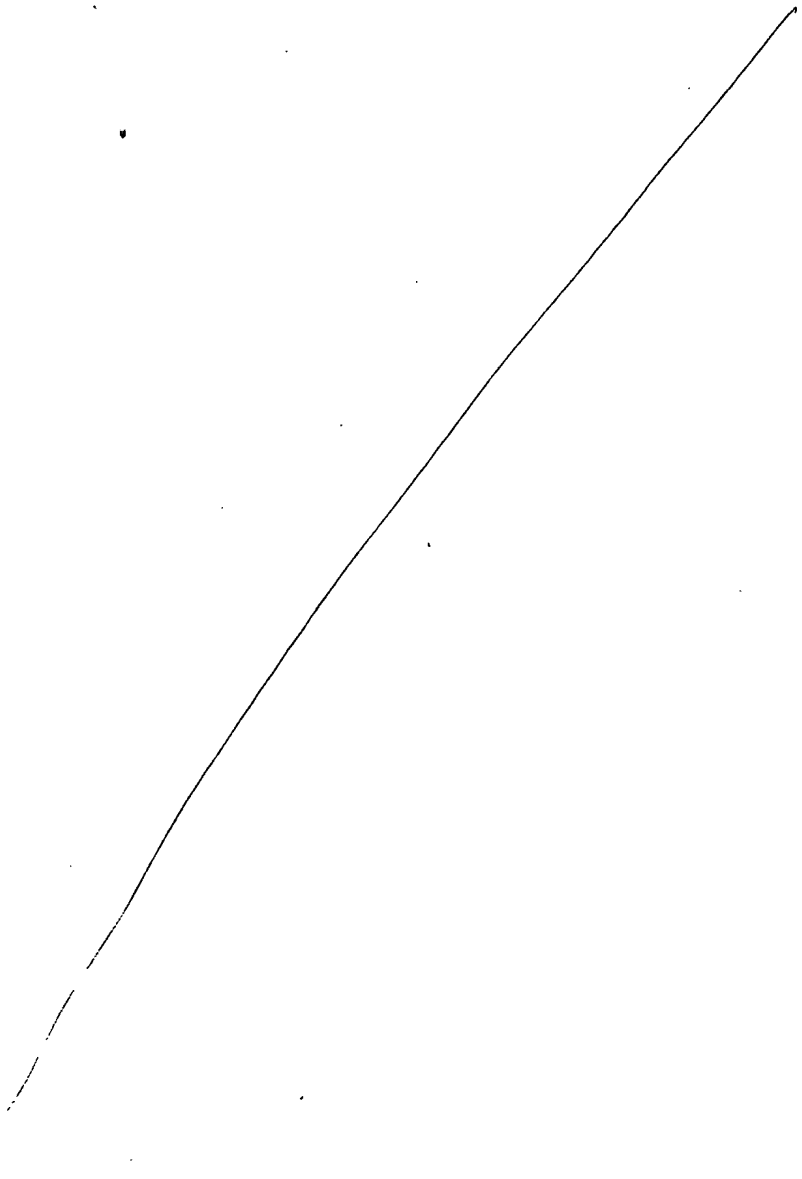
US 5,693,818 disclose the novel method to produce the single enantiomers of Omeprazole in neutral form, any isolated or characterized salt form and its analogues. The said patent particularly relates to sodium, calcium or magnesium salts of optically pure enantiomers of Omeprazole in 99.8% enantiomeric excess.

The process for the preparation of Esomeprazole comprises the reaction of 6-methoxy analog of Omeprazole with (R)-(-)-mandelic acid in chloroform to result the diastereomeric mixture, thus obtained mixture was subjected to reversed phase chromatography to get the more hydrophilic diastereomer. This was further reacted with aqueous sodium hydroxide solution in methanol using methyl formate to get the Esomeprazole with a purity of 94% enantiomeric excess and which was converted to sodium, magnesium or calcium salts in different solvents.

US 5,948,789 discloses the process for the preparation of single enantiomers or an enantiomerically enriched form of Omeprazole by an asymmetric oxidation of pro-chiral sulphide with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base. The process for the preparation of sodium salt of Esomeprazole was disclosed in the said patent, which comprises reacting sulphide intermediate of Omeprazole with (+)-diethyl L-tartrate, titanium (IV) isopropoxide and di isopropyl ethylamine using cumene hydroperoxide as an oxidizing agent in ethyl acetate. Then after to the resulting sulphoxide was added sodium hydroxide and upon crystallization yielded the Esomeprazole sodium salt with a purity of 99.8% enantiomeric excess.

WO 92/08716 discloses (+) enantiomer of Omeprazole in its neutral form as an amorphous solid.

WO 94/27988 discloses the preparation of the neutral form of the (-) enantiomer of Omeprazole, however it was obtained in the form of a syrup or oil which is unsuitable for pharmaceutical use because of the difficulty of handling an oil and incorporating it into solid pharmaceutical compositions.



USP 6,162,816 discloses the amorphous, Form-A and Form-B of crystalline forms of Esomeprazole and characterized by X-ray diffractograms. The said patent also discloses the process for the preparation of these amorphous and crystalline forms. The process for the preparation of amorphous form of Esomeprazole comprises, evaporating a solution of Esomeprazole in one or more organic solvents and further adding a solvent and evaporating further to afford the solid amorphous form.

The crystalline forms of Esomeprazole, which comprises the recrystallisation of neutral amorphous form of Esomeprazole in different solvents such as ethyl acetate, methylene chloride, and toluene to afford the said crystalline forms of Esomeprazole.

USP 6,369,085 discloses the crystalline forms of dihydrate and trihydrates of Esomeprazole magnesium salt. The dihydrate crystalline forms are designated as Form-A and Form-B. These crystalline forms have been characterized by X-ray diffractograms.

No other relevant patents have been disclosed the amorphous form of Esomeprazole and its salts.

The process for the preparation of amorphous form of Esomeprazole disclosed in the USP '816 is having some disadvantages as it is resulting in a solvated form. The high temperature and prolonged time is required for drying the obtained amorphous form, which in turn the nature of amorphous form is not retaining in the drying process.

Hence, the object of the present invention is to provide an alternate process to prepare amorphous form of Esomeprazole in neutral form in a simple, cost effective and commercially suitable process by overcoming the problems encountered in the prior art process.

The present process is more environment friendly and non-hazardous. The amorphous form of Esomeprazole of the present invention is resulted in a non-solvated form with free flowing solid.

The free flowing solids are in general preferred for pharmaceutical applications and the present inventive substance in amorphous form can be useful for pharmaceutical applications.

SUMMARY OF THE INVENTION

The present invention relates to a process for the preparation of an amorphous form of Esomeprazole. The process for the preparation comprises, resolution of Omeprazole sodium using Mandelic acid and a chiral titanium complex in a suitable solvent to result the titanium complex of mandelic acid salt of Esomeprazole. The said complex salt is reacted with sodium bicarbonate to afford Esomeprazole in residual form, which on further crystallization in a mixture of water and acetone resulted the amorphous form of Esomeprazole.

The present process is cost effective, environment friendly and commercially suitable. The inventive substance of present invention is non-solvated and free flowing solid, hence can be useful for pharmaceutical applications.

BRIEF DESCRIPTION OF ACCOMPANYING DRAWING

Fig. 1 is a characteristic X ray powder diffractogram of amorphous form of Esomeprazole.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a process for the preparation of amorphous form of Esomeprazole in a simple and reproducible manner.

Accordingly, the process for the preparation of an amorphous form of Esomeprazole, which comprises:

i) suspending Omeprazole sodium in ketone solvents such as acetone, ethyl methyl ketone, methyl isobutyl ketone or diethyl ketone, preferably acetone;

ii) adding diethyl D-tartrate, titanium (IV) isopropoxide and an organic base to the reaction mixture of step (i);

iii) adding L (+) mandelic acid to the reaction solution of step (ii) accompanied by stirring the mass for 15 minutes to 5 hours at a temperature of 25°C to a reflux temperature of solvent, preferably at a temperature of 35-40°C;

iv) filtering the separated solid of step (iii) to get the titanium complex of mandelic acid salt;

v) suspending the titanium complex of mandelic acid salt obtained in step (iv) in a mixture of 5 % sodium bicarbonate solution and a chlorinated solvent such as chloroform, dichloromethane, dichloroethane or carbon tetrachloride, preferably dichloromethane;

vi) distilling the solvent from the reaction solution of step (v) and accompanied by optional chiral purification in a solvent such as acetone , ethylacetate or acetonitrile to get the residual mass of Esomeprazole;

vii) recrystallisation of residual mass obtained in step (vi) in a mixture of water and acetone to afford the amorphous form of Esomeprazole.

The organic base mentioned in the step (ii) of the above process is selected from triethyl amine, di isobutyl amine, di tertiary butyl amine or tri isobutyl amine, di isopropyl ethylamine, di isobutyl ethyl amine, preferably tri ethyl amine.

The amorphous form of Esomeprazole obtained in the above process is dried in Buchi rota vapour flask under reduced pressure (750 mm/Hg) at a temperature of 25-30^{O}C under rotation, which resulted in a non-solvated and free flowing solid.

The present inventive substance is obtained in substantially free from crystalline solid.

The amorphous form of Esomeprazole of present invention can be well suited for pharmaceutical applications.

The present process for the preparation of an amorphous form of Esomeprazole is a simple, cost-effective and non-hazardous, hence it is better process over prior art references.

It is noteworthy to mention that Omeprazole sodium is prepared as per the process disclosed in the art. Omeprazole sodium is also outsourced in commercial quantities.

The novel process for the preparation of enantiomers of Omeprazole, pharmaceutically acceptable salts and hydrates is disclosed in our co-pending Indian Patent Application (Sent to IPO Chennai, India on 26.06.2002).

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

Reference Example:

Preparation of Omeprazole sodium:

Dissolved sodium hydroxide flakes (12.8 grams) in methanol (100 ml) and stirred for complete dissolution. Isopropyl alcohol (900 ml) was added and cooled the reaction mixture to 25-30^{O}C. Filter the solution through hi-flow bedded funnel and wash with isopropyl alcohol (100 ml). Charge Omeprazole (100 grams) to the clear filtered solution at an ambient temperature and stirred for 1-2 hours. The isolated product was filtered and

washed with isopropyl alcohol (200 ml) followed by petroleum ether (200 ml), dried at atmospheric temperature to afford the sodium salt of Omeprazole.

(Weight: 100 grams).

Example-1:

Preparation of Mandelic acid titanium complex salt of Esomeprazole:

Omeprazole sodium (100 grams) was suspended in Acetone (1.2 liter) and Diethyl D-tartrate (56.0 grams), Titanium (IV) isopropoxide (40.0 grams) and Triethylamine (82.0 grams) were added sequentially at a temperature of 35-40^{O}C. L (+) Mandelic acid (44.0 grams) was then added and further stirred for 15-30 minutes. The separated solid was filtered, washed with acetone (100ml) to afford the title compound.

[Weight: 80.0 grams, Chiral Purity: 93.4% (S-Isomer)]

Example-2:

Preparation of Esomeprazole:

Mandelic acid titanium complex salt of Esomeprazole (75.0 grams, obtained in Example-1) was suspended in a mixture of dichloromethane (375 ml), 5% sodium bicarbonate solution (375 ml), further stirred for 15-30 minutes. The dichloromethane layer was separated from the resulting solution and the solvent was distilled off completely to get the title compound in residual mass.

[Weight: 37.0 grams, Chiral Purity: 99.85% (S-Isomer)]

Example-3

Preparation of an amorphous form of Esomeprazole:

Esomeprazole (20.0 grams, obtained as per Example-2) was dissolved in a mixture of acetone (100 ml), water (200 ml) and further stirred for 15-30 minutes. The pH of the

mass was adjusted with caustic lye to 12 to13 accompanied by stirring for 30- 60 minutes. The reaction solution was subjected to carbon treatment at atmospheric temperature. Then, the pH was further adjusted to 7 to 8 with acetic acid. The reaction mass was cooled to a temperature of 5-10^{O}C and stirred for 1-2 hours to crystallize the solid mass. The solid mass was filtered, washed with water (100 ml) and dried under vacuum at a temperature of 25-30^{O}C to a constant weight.

(Weight: 7.0 grams, Chiral Purity: 99.94%)

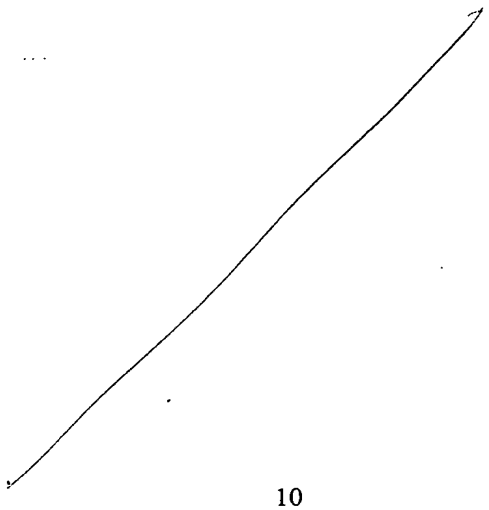
DETAILED DESCRIPTION OF ACCOMPANYING DRAWINGS:

Figure-1 is an amorphous Esomeprazole prepared according to the process of the present invention is characterized by its X-ray powder diffraction pattern.

The X-ray powder diffraction pattern shows no significant peaks, which is characteristic of amorphous Form.

Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees).

The X-Ray diffraction pattern of an amorphous form of Esomeprazole was measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.



WE CLAIM:

1. A process for the preparation of an amorphous form of Esomeprazole, which comprises:

i) suspending Omeprazole sodium in ketone solvents such as acetone, ethyl methyl ketone, methyl isobutyl ketone or diethyl ketone, preferably acetone;

ii) adding diethyl D-tartrate, titanium (IV) isopropoxide and an organic base to the reaction mixture of step (i);

iii) adding L (+) mandelic acid to the reaction solution of step (ii) accompanied by stirring the mass for 15 minutes to 5 hours at a temperature of 25^{O}C to a reflux temperature of solvent, preferably at a temperature of 35-40^{O}C;

iv) filtering the separated solid of step (iii) to get the titanium complex of mandelic acid salt;

v) suspending the titanium complex of mandelic acid salt obtained in step (iv) in a mixture of 5 % sodium bicarbonate solution and a chlorinated solvent such as chloroform, dichloromethane, dichloroethane or carbon tetrachloride, preferably dichloromethane;

vi) distilling the solvent from the reaction solution of step (v) and accompanied by optional chiral purification in a solvent such as acetone , ethylacetate or acetonitrile to get the residual mass of Esomeprazole;

vii) recrystallisation of residual mass obtained in step (vi) in a mixture of water and acetone to afford the amorphous form of Esomeprazole.

2. The amorphous form of Esomeprazole according to claim 1 is characterized by X-ray diffractogram and which is substantially in accordance with Figure (1).

3. The process according to claim 1 of step (i), wherein the said ketone solvent is acetone.

4. The process according to claim 1 of step (ii), wherein the base is selected from triethyl amine, di isobutyl amine, di tertiary butyl amine or tri isobutyl amine, di isopropyl ethylamine or di isobutyl ethyl amine.

5. The process according to claims 1 & 4, wherein the said base is di isopropyl ethylamine or tri ethyl amine.

6. The process according to claim 1 of step (iii), wherein the said reaction temperature is 35-40^{o}C.

7. The process according to claim 1 of step (v), wherein the said chlorinated solvent is dichloromethane.

8. The process according to claim 1 of step (vi), wherein the said ketone solvent is acetone for chiral purification.

9. A process for the preparation of an amorphous form of Esomeprazole is substantially as herein described and exemplified.

Dated: 27th the day of June 2002

Signed)_____

Dr. Manne Satyanarayana Reddy,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.

Dr. Reddy's Laboratories Limited

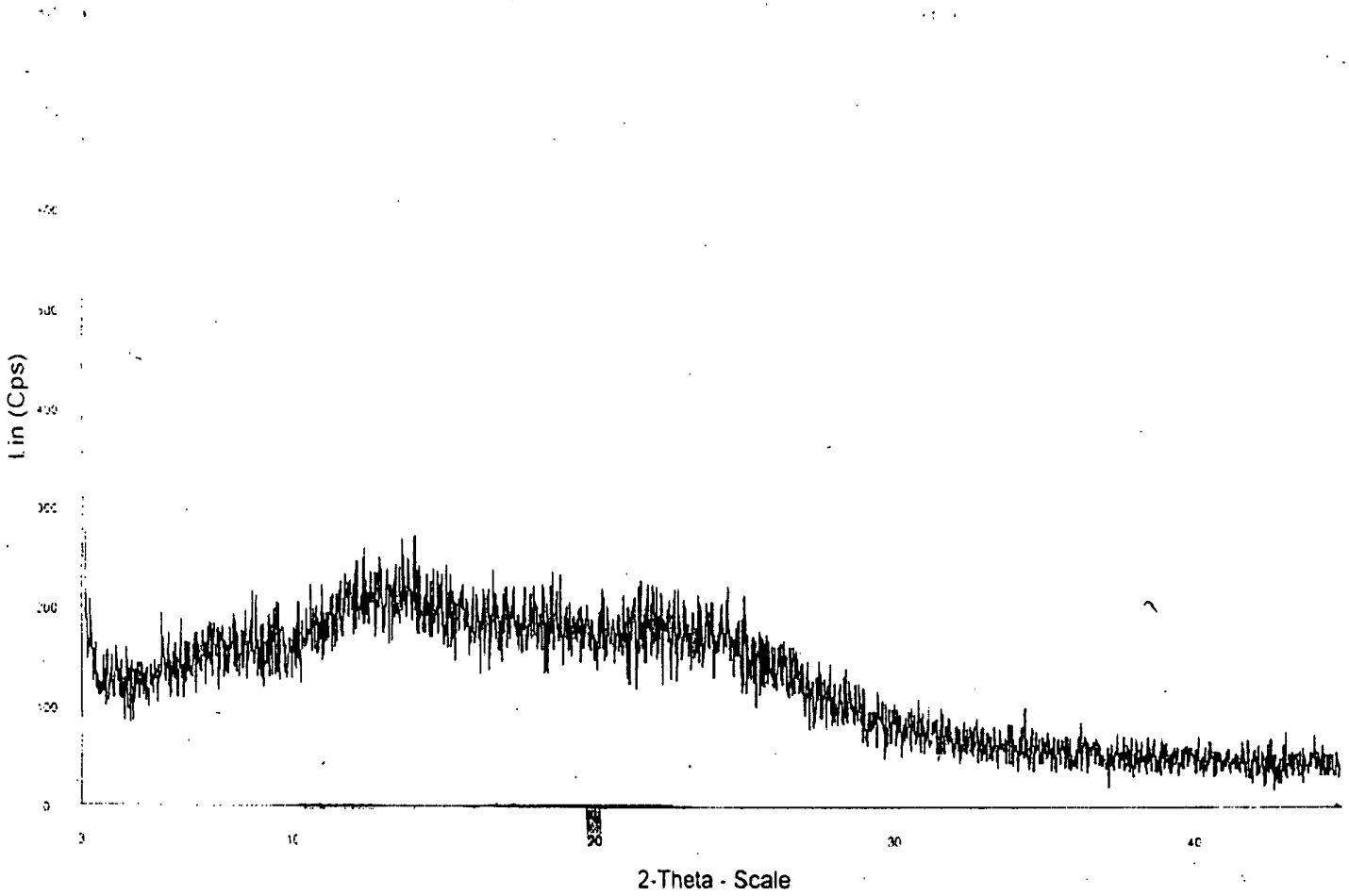


Fig.1